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Datasheet for the decision of 3 September 2019

Case Number: T 0421/14 - 3.3.01

Application Number: 05732613.4

Publication Number: 1732548

IPC: A61K31/44

Language of the proceedings: EN

Title of invention:
METHODS OF USING SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS

Patent Proprietor:
Acorda Therapeutics, Inc.

Opponents:
Synthon B.V.
neuraxpharm Arzneimittel GmbH

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)
RPBA Art. 12(4)

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It can be changed at any time and without notic

Keyword:
Sufficiency of disclosure - after amendment
Amendments - added subject-matter (no)
Evidence submitted with the statement of grounds of appeal - inadmissible (no)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
G 0001/15, T 1212/97

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Case Number: T 0421/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 3 September 2019

Appellant: (Opponent 1)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Appellant: (Opponent 2)	neuraxpharm Arzneimittel GmbH Elisabeth-Selbert-Str. 23 40764 Langenfeld (DE)
Representative:	Königer, Karsten Harmsen Utescher Rechtsanwalts- und Patentanwaltspartnerschaft mbB Neuer Wall 80 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	Acorda Therapeutics, Inc. 420 Saw Mill River Road Ardsley, NY 10502 (US)
Representative:	Goodfellow, Hugh Robin Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 December 2013 concerning maintenance of the European Patent No. 1732548 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 732 548 was granted with a set of 29 claims.

II. Two notices of opposition were filed, opposing the patent under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art and extended beyond the content of the application as filed.

III. In the course of the opposition proceedings, the patent proprietor submitted an amended main request and five auxiliary requests.

IV. Auxiliary request 2 contained, *inter alia*, the following independent claims:

> ***1.*** *A sustained release aminopyridine composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of aminopyridine.*
>
> ***8.*** *Use of aminopyridine in the manufacture of a sustained release composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of aminopyridine.*
>
> ***15.*** *A sustained release aminopyridine composition for maintaining a therapeutically effective concentration of an aminopyridine in a patient with multiple sclerosis,*

said composition to be administered as a stable dose treatment with a twice daily therapeutic dose of 10 milligrams of aminopyridine; and, wherein the sustained release aminopyridine composition has a therapeutically effective concentration for increasing the walking speed of a patient with multiple sclerosis.

V. The documents cited during the opposition proceedings included the following:

C3: Neurology 48, 817-821 (1997)

C10: Neurology 60 (Suppl 1), A167, S21.001 (2003)

C12: Neurology 45 (Suppl 4), A351, 684P (1995)

C16: Arch. Neurol. 51, 1136-1139 (1994)

C20: Declaration of Dr Ron Cohen (1 January 2013)

C21-Annex C: Lancet 373, 732-738 (2009)

C21-Annex D: Ann Neurol 68, 494-502 (2010)

C22-Annex G: Prescribing Information for Ampyra™ revised 2010 (pages 28-33 of 158)

C27: SEC Form S-1, Acorda Therapeutics, Inc. (September 2003)

C28: EP 2 377 536 A1

VI. The decision under appeal is the interlocutory decision of the opposition division, announced on 11 November 2013 and posted on 19 December 2013, rejecting the patent proprietor's amended main request and auxiliary request 1 and finding that the patent as amended in the form of auxiliary request 2 met the requirements of the EPC.

VII. According to the decision under appeal, certain claims of the main request and auxiliary request 1 contained added subject-matter. That objection did not apply to auxiliary request 2.

Since the therapeutic efficacy of the compositions according to the claims of auxiliary request 2 had been rendered credible and the opponents had not substantiated their assertion that not all aminopyridines were effective, the requirement of sufficiency of disclosure was met.

The claimed subject-matter was also novel over the disclosure of documents C10 and C12, *inter alia*.

Late-filed document C27 was not admitted into the proceedings. Document C28 (a divisional of the patent in suit) was admitted into the proceedings but could not be regarded as prior art anticipating the claimed subject-matter.

Document C3, which disclosed the twice-daily administration of 17.5 mg sustained-release 4-aminopyridine in the symptomatic treatment of multiple sclerosis, represented the closest prior art. Starting from the teaching of C3, the technical problem to be solved was the provision of a further treatment effective for the symptomatic treatment of multiple sclerosis, while reducing the incidence of side effects. That problem was solved by the treatment envisaged in the patent in suit, which involved the twice-daily administration of 10 mg of aminopyridine. That solution was not obvious, since the person skilled in the art would not have expected a treatment at reduced dosage to achieve the required therapeutic effect. Had the skilled person nevertheless decided to investigate the lower dosage, they would not have been able to appreciate the benefit of the claimed dosage regime using conventional statistical analysis.

VIII. The opponents (appellants) each filed an appeal against that decision, requesting the revocation of the patent.

IX. With its statement setting out the grounds of appeal, appellant-opponent 1 re-submitted documents C27 and C28 and filed further documents including the following:

C30: Goodman et al.: Poster

C30A: List of references cited by applicant for US application 11/102,559

C31: Goodman et al.: Slide show

X. With its reply to the statements setting out the grounds of appeal, the patent proprietor (respondent) filed an amended main request and three auxiliary requests and submitted further evidence including the following documents:

C32: Neurology, 46(4), 907-911 (1996)

C33: Declaration Dr Andrew Blight (15 September 2014)

XI. The independent claims of the **main request** read as follows:

> ***1.*** *A sustained release aminopyridine composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of aminopyridine.*
>
> ***6.*** *Use of aminopyridine in the manufacture of a sustained release composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of aminopyridine.*
>
> ***11.*** *A sustained release aminopyridine composition for maintaining a therapeutically effective concentration of an aminopyridine in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment with a twice daily therapeutic*

dose of 10 milligrams of aminopyridine; and, wherein the sustained release aminopyridine composition has a therapeutically effective concentration for increasing the walking speed of a patient with multiple sclerosis.

These claims are identical to claims 1, 8 and 15 of former auxiliary request 2 considered in the decision under appeal (see point IV. above). The other claims of the current main request (claims 2 to 5, 7 to 10, 12 and 13) are dependent claims.

XII. The independent claims of **auxiliary request 1** read as follows:

1. *A sustained release 4-aminopyridine composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of 4-aminopyridine.*

4. *Use of 4-aminopyridine in the manufacture of a sustained release composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 10 milligrams of 4-aminopyridine.*

7. *A sustained release 4-aminopyridine composition for maintaining a therapeutically effective concentration of 4-aminopyridine in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment with a twice daily therapeutic dose of 10 milligrams of 4-aminopyridine; and, wherein the sustained release 4-aminopyridine composition has a therapeutically effective concentration for increasing the walking speed of a patient with multiple sclerosis.*

The other claims of auxiliary request 1 (claims 2, 3, 5 and 6) are dependent claims.

XIII. With a further submission dated 30 September 2016, the respondent filed the following document, *inter alia*:

C30B: Supplemental Information Disclosure Statement (26 July 2012)

XIV. With a submission dated 10 January 2017, appellant-opponent 1 filed the following document, *inter alia*:

C38: Programme of the ACTRIMS/ECTRIMS 2002 conference

XV. Oral proceedings were held on 2-3 September 2019 in the absence of appellant-opponent 1, which had been duly summoned and, in accordance with Article 15(3) RPBA and Rule 115(2) EPC, was treated as relying only on its written case.

XVI. The appellants' arguments, as far as relevant to this decision, may be summarised as follows.

Sufficiency of disclosure

The patent in suit did not provide evidence of the therapeutic efficacy of the claimed dosage of 10 mg bid as the data reported lacked statistical significance.

Furthermore, the respondent's own data suggested that the desired therapeutic benefit was only attained in a small subpopulation of "responders" rather than in all multiple sclerosis patients. However, as the claims did not specify a step of initially identifying a patient as either a responder or non-responder, the claimed scope was incommensurately broad because it encompassed the treatment of patients not responding to aminopyridine.

These objections applied to the subject-matter of both the main request and auxiliary request 1.

As far as the main request was concerned, evidence was lacking that all aminopyridines, and in particular 3,4-aminopyridine, were therapeutically effective, let alone at a dosage as low as 10 mg bid. The patent in suit provided experimental data only for 4-aminopyridine. Moreover, document C16 taught that 3,4-aminopyridine was considerably less effective than 4-aminopyridine and had not shown any relevant benefit at a daily dosage between 40 and 80 mg.

Amendments - auxiliary request 1

The amendment introducing the term "stable dose treatment" into the independent claims was not supported by the application as filed.

Admission of evidence

Documents C30 and C31 were highly relevant and had been filed by appellant-opponent 1 with its statement setting out the grounds of appeal, in conformity with Article 12(1) and (2) RPBA. These documents originated from the respondent and were therefore known to it. The respondent had not objected to their admission in its initial reply to the statement of grounds.

Public availability of documents C30 and C31

C30 and C31 were copies of a poster and slides which had been presented by the respondent at a public conference. The correct standard of proof to be applied with regard to the issue of public availability before the effective date of the patent was the balance of probabilities. The burden of proof was on the respondent to substantiate its allegation that the

content of C30 and C31 was not identical to what had actually been presented to the public.

Novelty - auxiliary request 1

The disclosure of each of documents C10, C12, C27, C28 and C30 anticipated the claimed subject-matter.

Inventive step - auxiliary request 1

Document C27 was a promising and legitimate starting point for the person skilled in the art, who was not restricted to consulting scientific papers.
Starting from the information about clinical trials of 4-aminopyridine presented on pages 45 and 46 of C27, the objective technical problem to be solved was the provision of an effective treatment whereby walking speed in patients with multiple sclerosis would be improved. The skilled person would have had a reasonable expectation that all three dosages mentioned in C27, including the lowest dosage of 10 mg bid, would show therapeutic efficacy. Setting up a clinical study powered to confirm this expectation was routine work which would not have required inventive skill. It was incorrect to assume that the efficacy of the 10 mg bid dosage could only have been confirmed by the respondent's specific statistical method (the "responder analysis").

In a similar manner, the person skilled in the art investigating suitable dosages of 4-aminopyridine would have arrived at the claimed subject-matter starting from the teaching of document C10.

An assessment of inventive step starting from the disclosure of document C30 should also be taken into consideration.

XVII. The respondent's arguments, as far as relevant to this decision, may be summarised as follows.

Sufficiency of disclosure

The data presented in Example 5 of the patent in suit and its associated figures showed that the claimed dosage regime was effective and safe. Specifically, the responder analysis developed and carried out post hoc by the inventors, which was based on consistency of response rather than on magnitude of response, revealed a significantly higher number of responders in the group treated with 4-aminopyridine than in the placebo group, without a difference in efficacy between the three dosages tested. These results had also been confirmed by subsequent phase 3 clinical studies.

It was a commonly recognised phenomenon that there were subpopulations of non-responders to many treatments. However, medical uses were nonetheless patentable, as the technical contribution resided in the therapeutic benefit for a substantial proportion of the treated population. It was also appropriate and usual to claim the treatment of an individual patient while the efficacy of a treatment could only be demonstrated in a population of patients.

The burden of proof was on the appellants to substantiate their allegation that aminopyridines other than 4-aminopyridine were not effective at a twice-daily dose of 10 mg. Document C16 cited by the appellants confirmed, in fact, that 3,4-aminopyridine did have a therapeutic benefit, and certainly did not teach that this compound was ineffective when administered according to the claimed dosage regime.

Amendments - auxiliary request 1

It would be recognised in the art that the term "stable dose" referred to the final maintenance dose (effective amount) on which a patient remained during the course of a treatment, as opposed to lower doses which might have been administered during an initial dose-escalation period. This meaning was made clear in paragraph [0015] and throughout Example 5, which provided the required basis for the relevant technical feature in the application as filed.

Admission of evidence

Documents C30 and C31 should have been presented by the appellants during the proceedings before the opposition division. Their prior-art status and potential relevance could not be established without further investigation. In any case, they did not *prima facie* appear to be more relevant than document C27.

Public availability of documents C30 and C31

There was reasonable doubt that documents C30 and C31, which both related to disclosures allegedly presented at a public conference, were identical to what had been presented, and formed part of the prior art. C30 and C31 were unlikely to be copies of any visual aids actually used at the conference, as suggested by the appearance and inaccurate content of these documents. There was no evidence on file of what the audience had understood from the presentations, and no record of what the presenter(s) had said.

Novelty - auxiliary request 1

None of documents C10, C12, C27 and C30 cited by the appellants against novelty specifically disclosed the efficacy of 4-aminopyridine, when administered twice

daily in a dose of 10 mg, for increasing walking speed. The person skilled in the art would have realised that the dose-escalation study reported in C10, C27 and C30 had not been powered to allow the efficacy of each individual dose of 4-aminopyridine to be assessed. The appellants' "poisonous divisional" argument with regard to C28 could not be right as a matter of principle.

Inventive step - auxiliary request 1

Document C3 should be regarded as the closest prior art. Since this document taught the person skilled in the art to use a higher dosage of aminopyridine and did not provide any pointer to lowering the dosage to 10 mg bid, the claimed subject-matter involved an inventive step.

The appellants' new line of argument assessing inventive step starting from the disclosure of document C30 should not be admitted into the proceedings as it amounted to a change of the appellants' case at a late stage of the proceedings.

In any case, none of documents C10, C27 or C30 cited by the appellants against inventive step disclosed drug efficacy for a dosage of 10 mg bid, the lowest dosage mentioned in these documents. Nor did they suggest that the therapeutic benefit of the 10 mg bid dosage was comparable to that achieved with higher dosages while the incidence of adverse effects was lower.

The technical problem to be solved was thus to provide an improved therapy for MS patients.

The person skilled in the art would not have expected the dosage of 10 mg bid to be effective, nor had it been a simple matter of routine to confirm the efficacy

of this dosage. Rather, the inventors had designed a parallel-arm study and had only been able to ascertain the optimum dose by employing a novel statistical methodology based on the consistency of the subjects' response to the drug. As the inventors' study design and subsequent analysis had been non-obvious measures, their result was not obvious either.

XVIII. Appellant-opponent 1 and appellant-opponent 2 requested that the decision under appeal be set aside and that European patent No. 1 732 548 be revoked.

XIX. The respondent (patent proprietor) requested that the appeals be dismissed and that the patent be maintained on the basis of the claims of the main request, or in the alternative, of any of auxiliary requests 1 to 3, all filed with the reply to the statements setting out the grounds of appeal.

The respondent also requested that documents C30 and C31 not be admitted into the proceedings.

Reasons for the Decision

1. Admissibility of the appeals

The appeals comply with Articles 106 to 108 EPC and Rule 99 EPC and are therefore admissible.

2. Sufficiency of disclosure - main request

2.1 The patent in suit seeks to provide a sustained-release oral dosage form of an aminopyridine, most preferably 4-aminopyridine (also called dalfampridine or fampridine), which can be used in the treatment of patients suffering from multiple sclerosis (see paragraphs [0001] and [0009] of the patent in suit and

paragraphs [0002] and [0010] of the application as filed).

2.2 The independent claims of the main request specify a dosage regime involving twice-daily treatment with 10 mg of sustained-release aminopyridine, for increasing walking speed. The board considers that the wording of claim 11 does not introduce any limitation not already provided by the term "stable dose treatment" and by the specified dosage of 10 mg bid.

2.3 These claims all relate to a further medical use. According to the established case law of the Boards of Appeal, attaining the claimed therapeutic effect is regarded as a functional technical feature of such claims. In order to meet the requirement of sufficiency of disclosure of Article 83 EPC, the therapeutic efficacy of the composition and dosage regime for the claimed therapeutic indication must therefore be credible.

2.4 It was not in dispute that the person skilled in the art is capable of preparing sustained-release dosage forms of aminopyridines. All objections raised by the appellants with regard to sufficiency concerned the credibility of the alleged therapeutic efficacy. The respondent relied, in this respect, on the data and analysis of a clinical trial (the "MS-F202" trial), as presented in Example 5 of the application as filed.

2.5 Example 5 (see the application as filed, paragraphs [0101] to [0133], and the associated figures) relates to a phase 2, 20-week, double-blind, placebo-controlled treatment study in 206 subjects diagnosed with multiple sclerosis (MS), designed to investigate the safety and efficacy of three dose levels of sustained-release 4-aminopyridine. The dosages administered in this study

during a 12-week stable-dose treatment period were 10 mg bid, 15 mg bid and 20 mg bid. The primary efficacy endpoint was an increase, relative to baseline, in walking speed on the "Timed 25 Foot Walk".

Non-responders

2.6 As acknowledged in the application as filed (see paragraph [0079]), it was known that only a proportion of patients, estimated to be about one third, responded to treatment with 4-aminopyridine. The existence of a population of non-responders was also confirmed by the inventors' own results reported in Example 5.

Aminopyridines are potassium channel blockers whose proposed mechanism of action is the restoration of conduction in demyelinated axons. Given the highly variable pathology of MS, only a proportion of MS patients would be expected to possess axons of appropriate functional relevance susceptible to this mechanism of action, which would explain the occurrence of non-responders (see the application as filed, paragraphs [0005] and [0079]).

Contrary to the appellants' view, the existence of non-responders is not a reason to deny sufficiency of disclosure, and the treatment of non-responders does not have to be excluded or disclaimed.

The existence of a substantial proportion of patients who are non-responders is a common phenomenon which is observed with drugs in many treatment areas, such as diabetes, migraine or cancer treatment. It is common practice to treat patients with a drug and change their medication should it turn out that they do not respond to the treatment.

If it can be shown that a relevant proportion of patients benefits from a treatment and that it has

acceptable safety, the criterion of sufficiency of disclosure is met since the person skilled in the art has the necessary technical information to perform the treatment.

Therapeutic utility of 10 mg bid 4-aminopyridine ("fampridine")

2.7 As explained in the respondent's reply to the statements setting out the grounds of appeal (section 4) and in document C32 (figures), multiple sclerosis (MS) is a disease that is characterised by unusual variability in the occurrence of symptoms, with frequent episodes of relapse and remission being common. Progression of disability may occur, at variable rates, from onset or from a later stage, with or without plateau or remission phases. As a result of the fluctuating nature of MS symptoms, recognising the clinical benefit of therapies is particularly difficult. This is acknowledged in the application as filed (paragraph [0081]), which states:

> *"Given the often large variations in function experienced by people with MS, it is difficult for the subject or a trained observer to separate a treatment-related improvement from a disease-related improvement without the element of consistency over time. Consistency of benefit might therefore be expected to be a more selective measure of true treatment effect than magnitude of change".*

2.8 According to the respondent, presumably due to these fluctuations, the pre-planned first analysis of the data obtained in the clinical trial of Example 5 for the primary efficacy endpoint (percent change in average walking speed during the 12-week stable-dose period relative to baseline) did not show statistically significant differences between any

of the 4-aminopyridine groups and the placebo group (see paragraphs [0103], [0114] and Figure 3 of the application).

That was also the case for a second approach (the "protocol-specified responder analysis"), which identified successful response for each subject as improvement in walking speed (percent change from baseline) of at least 20% (see paragraphs [0104], [0115] and Figure 4 of the application).

2.9 To overcome this difficulty, and following the rationale explained in point 2.7 above, the inventors introduced an adapted evaluation method which focused on the consistency of response rather than the intensity of response to the drug (the post-hoc responder analysis).

This post-hoc analysis identified likely responders as subjects exhibiting a faster walking speed for at least three of five assessment visits during the double-blind stable-dose treatment period as compared with the maximum value observed among a set of five non-treatment visits - four before treatment and one after discontinuation of treatment (paragraph [0105] of the application). Furthermore, the proportions of subjects meeting this criterion in the pooled fampridine groups and in the placebo group were compared.

2.10 This analysis revealed the existence of a subset of subjects who responded to the drug with clinical meaningfulness (paragraph [0120] of the application). The number of subjects who met the post-hoc responder criterion in the pooled fampridine-treated group was 58 (36.7%) versus 4 (8.5%) apparent "responders" in the placebo-treated group, and this difference was statistically significant ($p<0.001$) (paragraph [0122]

and Figure 8). The post-hoc responder rates based on consistency of improved walking speed were significantly higher in all three active-dose groups (35%, 36% and 39%) compared to placebo (9%; p<0006 for each dose group, adjusting for multiple comparisons) (see paragraph [0121] and Figure 7). The mean improvement in walking speed for the fampridine responders was more than 24% (paragraph [0107] and Figure 10). No notable differences in efficacy were found between 15 mg bid and 10 mg bid among responders (see paragraph 0132]). It was also reported that serious adverse effects did not occur in the 10 mg bid group (paragraph [0133]).

2.11 While the appellants, referring to the results summarised in point 2.8 above, disputed that therapeutic efficacy had been demonstrated, the board considers that the explanation for the initial finding of lacking statistical significance, the rationale given for the post-hoc methodology and the respective results presented in Example 5 of the application (see points 2.9 and 2.10 above) are convincing and are also sufficient to have rendered the alleged therapeutic efficacy and safety of 4-aminopyridine at 10 mg bid credible on the effective date of the patent.

Therapeutic efficacy across the scope claimed

2.12 The data presented in the application as filed and the corresponding passages of the patent in suit only relate to 4-aminopyridine, but not to other aminopyridines. Without experimental data it is indeed not possible to ascertain whether the specific dosage of 10 mg bid would be acceptably effective and safe in the case of other aminopyridines. The appellants' already plausible objection in this regard was further substantiated by the findings of document C16, which

provides a direct comparison between 4-aminopyridine and 3,4-aminopyridine.

The authors of C16 reported that 4-aminopyridine had a more favourable toxicity profile and was also more effective than 3,4-aminopyridine, including for ambulation (see C16: page 1136, "Results" and "Conclusion"; and page 1139, column 2, lines 1 to 19). While the capsules used according to C16 were immediate-release rather than sustained-release formulations, this does not render the comparison meaningless for the present purpose, since both drugs were administered in immediate-release form and a considerable difference in efficacy was observed. In the studies described in C16, the daily doses of 3,4-aminopyridine were twice as high as the doses of 4-aminopyridine (see C16: second page, "Patients and Methods", last sentence, indicating that identical capsules containing either 5 mg 4-aminopyridine or 10 mg 3,4-aminopyridine were used). The mean daily doses of 4-aminopyridine and 3,4-aminopyridine were 23 mg (range 10 to 35 mg) and 46 mg (range 20 to 70 mg), respectively (see C16: page 1138, column 1, first paragraph).

These are valid reasons why the dosage regime of 10 mg bid cannot simply be extrapolated to further aminopyridines.

Conclusion

2.13 For the reasons set out in point 2.12, the subject-matter of the independent claims of the main request is insufficiently disclosed within the meaning of Article 83 EPC, as far as the scope covering aminopyridines other than 4-aminopyridine is concerned.

3. Amendments - auxiliary request 1

3.1 Independent claims 1, 4 and 7 are based on claim 3 of the application as filed, defining an effective amount of 10 mg aminopyridine, to be administered twice daily in the form of a sustained-release composition, for increasing the walking speed of a patient with multiple sclerosis (see also paragraph [0016] of the application). It was not in dispute that 4-aminopyridine is the most preferred aminopyridine in the application as filed (see paragraph [0010]).

3.2 Since multiple sclerosis is a chronic disease the treatment of one of its symptoms envisaged in the application would be expected to continue over a period of time. As generally disclosed in paragraph [0015] of the application as filed, the composition can be used

> *"for building up a level and or maintaining a therapeutically effective concentration of an aminopyridine in the patient by twice daily dosing"*.

The latter use describes the concept of stable-dose treatment, which involves administering the same dosage over consecutive days.

3.3 This concept was applied in the clinical study described in Example 5 and is mentioned in various passages (see, for instance, paragraphs [0102], [0104], [0112] to [0115] and [0118]) of the application as filed. After a dose-escalation phase, the subjects underwent a stable-dose treatment period of 12 weeks, the aim of the study being to evaluate the effect of the drug during this treatment period.

3.4 The person skilled in the art reading the application as filed would readily identify this general concept (which is also in line with known standard practice of

medication) and would not consider it to be inextricably linked to a duration of twelve weeks (the 12-week period in Example 5).

3.5 Contrary to the argument by appellant-opponent 1, the deletion of the expression "effective amount" is not objectionable, since, firstly, the wording "administered as a stable dose treatment ... in a therapeutic dose" still means that an effective amount is administered, and, secondly, the specified amount remains the same in any case, namely 10 mg twice daily.

3.6 In conclusion, the board finds that the subject-matter of independent claims 1, 4 and 7 of auxiliary request 1 does not extend beyond the content of the application as filed (Article 123(2) EPC).

4. Sufficiency of disclosure - auxiliary request 1

4.1 The independent claims of auxiliary request 1 differ from those of the main request in that "aminopyridine" has been restricted to "4-aminopyridine".

4.2 As a consequence, the objection according to point 2.12 above does not apply to the claims of auxiliary request 1. For the same reasons as set out in points 2.1 to 2.11 above, the claimed subject-matter meets the requirement of sufficiency of disclosure (Article 83 EPC).

5. Admission of documents C30 and C31

5.1 Documents C30 and C31 were filed, for the first time, by appellant-opponent 1 with its statement setting out the grounds of appeal, in conformity with Article 12(1) and (2) RPBA. Pursuant to Article 12(4), second clause, RPBA, these documents are thus, as a

rule, to be taken into account in the appeal proceedings.

5.2 Pursuant to Article 12(4), first clause, RPBA, the board has the discretionary power to hold evidence to be inadmissible which could (and should) have been presented in the proceedings at first instance.

5.3 However, the argument that C30 and C31 had been available to the appellants at an earlier time did not constitute a compelling reason for the board to hold these documents inadmissible pursuant to Article 12(4) EPC.

6. Admission of document C27

6.1 The opposition division did not admit late-filed document C27 into the proceedings, since its prior-art status was in dispute and no evidence regarding this issue had been presented by the opponents (see the decision under appeal, point 5 of the Reasons).

6.2 The document was re-submitted by appellant-opponent 1 with its statement setting out the grounds of appeal, in conformity with Article 12(1) and (2) RPBA, together with evidence regarding its publication. In these appeal proceedings, the respondent did not dispute the public availability of C27 on the effective date of the patent and did not maintain the objection against its admission. Hence, the board saw no reason for holding C27 inadmissible pursuant to Article 12(4) RPBA.

7. Public availability of documents C30 and C31

7.1 Relying on documents C30A and C38 (see P308 on pages 25 and 48) *inter alia*, the appellants contended that the poster C30 and the slide presentation C31 (both undated) had been presented to the public at the

7th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis and 18th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS/ECTRIMS) which took place in Baltimore, Maryland (USA) on 18-21 September 2002, i.e. before the effective date of the patent in suit.

7.2 C30 and C31 are identical to references CC15 and CC16 listed in document C30A ("List of References cited by Applicant"), which mentions that these were presented at the ACTRIMS/ECTRIMS conference in September 2002. The respondent itself filed both documents at the US Patent and Trademark Office (USPTO) in 2012 (see C30B and the reply to the statements setting out the grounds of appeal, footnote on page 13), together with the document list C30A, as part of an Information Disclosure Statement (IDS) for the case file of US application number 11/102,559 (see the respondent's letter dated 30 September 2016, point 1.4). The documents were downloaded by appellant-opponent 1 from the USPTO's online register (PAIR).

7.3 The respondent disputed, however, that the content of C30 and C31 was indeed identical to what was presented at the ACTRIMS/ECTRIMS conference.

According to the respondent, these documents had been filed at the USPTO years after the conference in question. At that point in time, it was not known beyond reasonable doubt to the US attorney who wrote C30B (the accompanying letter submitted to the USPTO together with C30A, C30 and C31) whether C30 and C31 really had been presented at the conference of 2002.

As explicitly stated in document C30B, identification of the references in C30A was not meant to be construed as an admission that they were prior art.

Furthermore, C30B included the following statement:

> *"On information and belief, after reasonable inquiry, the poster and slide presentation listed as References CC15 and CC16, respectively, in the attached List of References Cited, were presented at the ACTRIMS 7th Annual Conference and ECTRIMS 18th Congress on September 18-21, 2002. Applicants reserve the right to correct this information should further information show such correction is warranted."*

The respondent also argued that, while there was no evidence from the appellants to show that C30 and C31 were an accurate description of what was disclosed at the ACTRIMS/ECTRIMS conference, the appearance and inaccurate content of C30 and C31 suggested that they were not the visual aids actually used at the conference.

Furthermore, the respondent contended that the presentation of slides or of a poster in both cases also involved an aural element. It could not be established what an audience would have understood in each case in the light of the oral discussion with the presenter.

7.4 It was a disputed subject among the parties what standard of proof was required regarding the public availability of documents C30 and C31.

7.5 According to the case law of the Boards of Appeal, the usual standard of proof is the overall balance of probabilities.

7.6 The stricter standard of proof "beyond all reasonable doubt" has been used, exceptionally, in cases of public prior use where all the supporting evidence lay within the power and knowledge of the opponent. (The issue of

public prior presentation of posters or slides has, as a rule, been assessed in line with the requirements for public prior use).

In these appeal proceedings, that condition is not fulfilled since C30 and C31 alleged to be public prior disclosures are the patent proprietor's (respondent's) own documents.

7.7 The respondent also argued that both C30 and C31 involved "ephemeral" oral presentations and that, therefore, the standard of proof for ascertaining the content of the oral disclosure must be higher (see decision T 1212/97, point 2 of the Reasons).

The board considers that, at least in the case of the poster C30, this argument is not convincing, since the disclosure relied on by the appellants is the printed and therefore "fixed" content of the poster displayed, whereas T 1212/97 cited by the respondent deals with the alleged information content of an orally delivered lecture (without a written complement in the form of a script, handout or later publication).

7.8 The question of whether citing a reference in an IDS is, as a matter of principle, an acknowledgement that it is prior art is irrelevant to the issue under discussion. What is more relevant is that the respondent explicitly stated in C30B that to the respondent's best knowledge ("on information and belief and after reasonable inquiry"), C30 and C31 (designated "CC15" and "CC16" in C30A) were presented at the ACTRIMS/ECTRIMS conference of 2002.

7.9 In the case of the poster C30, the respondent's own statement in C30B leaves little room for doubt that this poster was indeed displayed, whereby the entirety of the information printed on the poster was disclosed

to the public. In this situation, it was for the respondent to show that this was not the case.

7.9.1 The respondent did not provide first-hand evidence from witnesses, in particular the presenters themselves, regarding the actual printed content of the poster presented at the ACTRIMS/ECTRIMS conference. Instead, the respondent's argument is based on circumstantial evidence. Pointing out certain errors in the technical content of document C30 as well as typographical and formatting errors, the respondent contended that such errors were not expected to occur in a presentation by professional scientists and that the poster therefore could not have been presented in the version shown in C30. C30, retrieved at a later point in time, might simply have been a draft.

7.9.2 This argument is speculative and not persuasive, even less so since it is the respondent itself which should know the exact circumstances. The board also notes that the respondent never retracted its statement in C30B. As a consequence, on the overall balance of probabilities, the poster C30 is considered to form part of the prior art.

7.10 The situation is different in the case of C31, due to C31 being a slide presentation. Slides are typically used as the basis of an oral presentation. No evidence is on file from which it may be inferred that the slides of C31 were handed out in printed form at the conference, or that all of the slides were shown to an audience. There is no evidence regarding the manner or speed of the oral presentation. The printed content of the slides alone is insufficient for establishing what precisely the members of the audience would have understood, and retained, from an oral presentation at the ACTRIMS/ECTRIMS conference during which all or

some of the slides of C31 may have been shown. Hence, and irrespective of the standard of proof applied, the content of C31 cannot be considered to be prior art.

8. Novelty - auxiliary request 1

8.1 Since the therapeutic efficacy of 4-aminopyridine administered at 10 mg bid is a functional technical feature of claims 1, 4 and 7 (see point 2.3 above), this feature must be taken into account in the assessment of novelty and inventive step.

This means that a prior-art disclosure can only be novelty-destroying if it discloses this therapeutic efficacy. Thus, the appellants' argument that any prior treatment carried out inherently would be novelty-destroying must fail.

8.2 During the development of the treatment which is the subject of the claims of auxiliary request 1, the respondent carried out the following two clinical studies (as set out in the declaration C20 filed by the respondent and as mentioned in C27).

- "MS-F201" (completed in 2001): a double-blind phase 2 clinical trial of sustained-release 4-aminopyridine designed to assess safety and determine favourable dose levels and involving a total of 36 subjects and dosages from 10 mg bid to 40 mg bid;
- "MS-F202" (initiated in 2003, completed in 2004): a late phase 2 clinical trial assessing the efficacy and safety of three doses of sustained-release 4-aminopyridine (10, 15 and 20 mg bid). This is the trial with 206 subjects discussed in example 5 of the patent in suit.

Documents C10, C27 and C30 cited by the appellants against novelty all relate to data obtained in the MS-F201 trial. C27 also mentions the MS-F202 trial.

8.3 C10 is a conference abstract reporting on the MS-F201 trial. This was an escalating-dose study of a sustained-release formulation of 4-aminopyridine, starting from 20 mg/day (10 mg bid), increased in weekly increments of 10 mg/day to 80 mg/day administered orally to 25 multiple sclerosis patients. 11 patients received placebo treatment. The results relating to therapeutic efficacy are described as follows:

> *"The fampridine-SR group showed statistically significant improvement from baseline compared to placebo in functional measures of mobility (timed 25 walking speed; p = 0.04) and lower extremity strength (manual muscle testing; p= 0.01). Dose response curves showed increasing benefit in both measures in the 20 to 50 mg/day range."*

It cannot be inferred from this statement in a direct and unambiguous manner that a therapeutic benefit for walking speed was obtained, specifically, with the (lowest) dosage of 20 mg/day (10 mg bid). The last sentence is, for instance, also consistent with a situation in which there is no improvement in efficacy relative to placebo at 20 mg/day but increasing improvement from 30 to 50 mg/day. Hence, the disclosure of C10 does not anticipate the subject-matter of claims 1, 4 and 7.

8.4 Document C12 is an abstract relating to an earlier dose-finding study of a slow-release formulation of 4-aminopyridine carried out with 12 MS patients. While, *inter alia*, a dosage of 10 mg bid is mentioned, no observations relating to walking speed are reported.

C12 concludes that daily doses up to 50 mg can be safely administered to patients, and that further studies to determine efficacy are warranted. Thus, the disclosure of C12 does not anticipate the subject-matter of claims 1, 4 and 7.

8.5 Document C27 (pages 45 and 46) reports results from the MS-F201 trial and mentions the MS-F202 trial, which was ongoing at the time when C27 was published. Since C27 does not disclose any data of the MS-F202 trial, only the passage relating to the MS-F201 trial is relevant for the assessment of novelty (see C27: paragraph bridging pages 45 and 46 and Figure 2).

C27 explains that a total of 25 of the 36 subjects of the MS-F201 trial received fampridine-SR in doses increasing from 10 mg bid to 40 mg bid over eight weeks of treatment, while 11 subjects received placebo over the same period. C27 states:

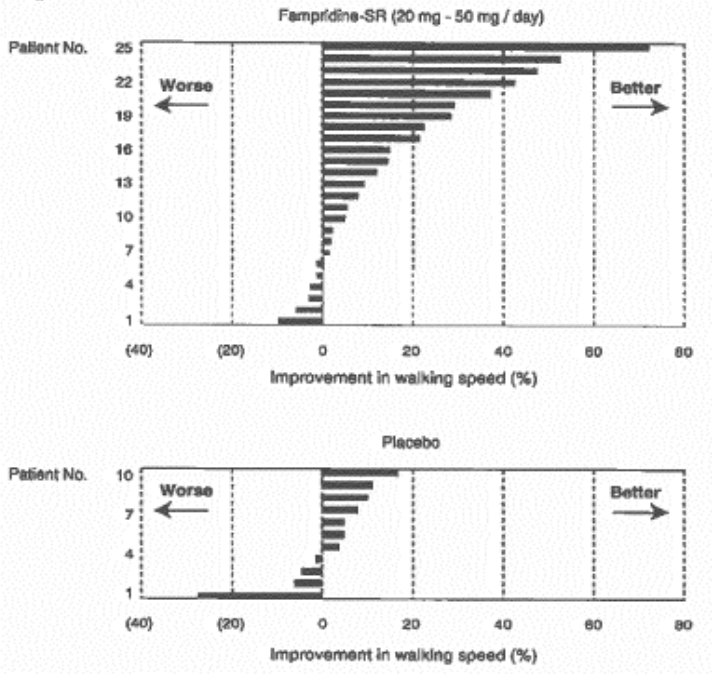
> *"Most of the improvement in strength and walking speed was apparent within the first three weeks of the Fampridine-SR treatment at doses from 10 to 25 mg twice a day".*

This corresponds to the statement in document C10 mentioning increasing benefit in the 20 to 50 mg/day range, which is however inconclusive regarding the efficacy of the 10 mg bid dosage (see point 8.3 above).

Figure 2 of C27 is a histogram showing the improvements in walking speed (%) observed in the 25 individual subjects receiving fampridine. The percent values represent the average response of each subject over the first four treatment weeks (see C27: page 46, lines 3 to 4). During this time, each subject was treated with escalating doses from 10 to 25 mg bid (20 to 50 mg/day). As only the average value is shown Figure 2 does

not provide any response data which can be attributed specifically to the 10 mg bid dosage.

Figure 2: Change in Walking Speed During the First Four Weeks of Treatment



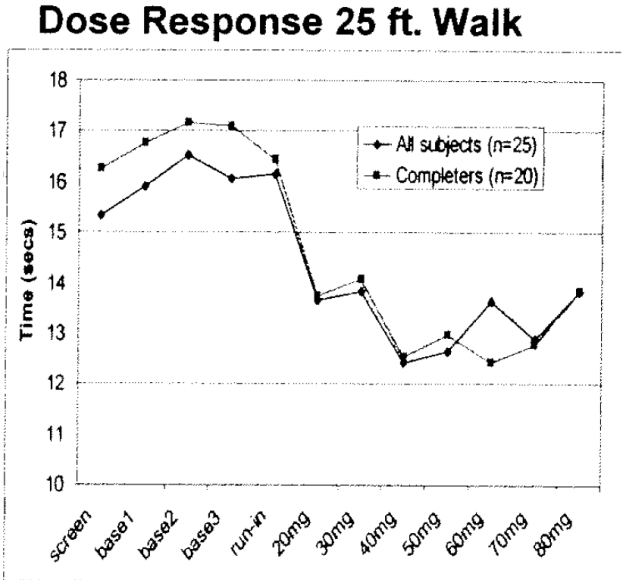
Consequently, document C27 does not disclose therapeutic efficacy for the 10 mg bid dosage and does not anticipate the subject-matter of claims 1, 4 and 7.

8.6 Document C30, the poster which was displayed at the 2002 ACTRIMS/ECTRIMS conference, also presents data from the MS-F201 trial.

8.6.1 The abstract section of C30 is largely identical to the text of C10, including the inconclusive statement that dose-response curves showed increasing benefit in the 20 to 50 mg/day range (see point 8.3 above). The section "conclusions" states in a similar manner that there was "evidence of dose-response in 20-40 mg/day range". This statement alone does not imply that therapeutic efficacy was indeed observed at the individual dosage of 10 mg/bid.

8.6.2 The histogram figure "25 Foot Walk-Change in Speed" presents the individual subjects' results in the same manner as Figure 2 of C27, although the figure in C30 appears to be erroneous in that it shows, contrary to the cohort sizes indicated in the section "Demographics", 26 rather than 25 values for the aggregated (20-50 mg/day) fampridine group and 12 rather than 11 values for the placebo group. In any case, as set out in point 8.5 above, the presentation of average values across several dosages chosen for this graph does not permit any conclusion to be drawn regarding the therapeutic efficacy of the 10 mg bid dosage regime.

8.6.3 A further figure in C30 is entitled "Dose Response 25 ft. Walk". This curve contains only data from patients administered the drug and not those given placebo. The walking time in seconds indicated in this curve is the mean value of all participants receiving fampridine treatment.



The appellants argued that the drop from about 16 to about 13.5 seconds between run-in and 20 mg disclosed treatment efficacy at 20 mg/day (10 mg bid). While the appellants did not demonstrate why this drop would be

regarded as statistically significant, they contended that the skilled person had no reason to question the meaningfulness of the data presented in C30. Also, the claims covered any increase in walking speed, and average changes smaller than 20% in a group of subjects could well be indicative of improvement.

In fact, as pointed out by the respondent, there are several serious reasons to doubt the significance of the drop depicted in the dose-response curve.

In particular, the skilled person studying C30 would be well aware of the fluctuations in the occurrence and severity of symptoms that are characteristic of MS (see point 2.7 above) and of the limited number of participants in the trial in question, which was designed merely as a preliminary dose-ranging study (see C30: Methods). Accordingly, the abstract section of C30 notes that the primary object of the study was to determine the safety and tolerability of escalating doses, while the secondary aim was to explore efficacy over a broad dose range. Thus, it is not credible that the study was powered to enable conclusions about the efficacy of individual doses to be drawn.

The dose-response curve itself shows fluctuations in the baseline average (see the first five values determined before the start of the drug administration) of up to 1-1.5 seconds, which would be attributed to "noise".

While the absolute values in seconds observed in the placebo group are not indicated, C30 discloses that relative changes of up to 18% increase in walking speed were observed in the placebo group during the initial low-dose treatment period (see C30: Results Summary and 25 Foot Walk-Change in Speed histogram), which further

corroborates the existence of fluctuations in the individuals' symptoms which are unrelated to treatment.

Only the mean values of all treated subjects are shown in the dose-response curve of C30, while no information about the variability of individual measurements is provided.

It can also be inferred from the values shown in the histogram figure for the relative change in speed ("25 Foot Walk-Change in Speed") that there was a large degree of inter-patient variability.

The dose-response curve relates to a different parameter as it indicates the absolute improvement in walking speed, which would have a different relative impact depending on the baseline walking speed of each subject. Without knowledge of each subject's individual measurements, it is not possible to know how the absolute and relative changes compare.

In view of these considerations, in particular the low number of trial participants and the manner in which the data is presented, which lacks pertinent information (such as a comparison with the placebo group), the board is not convinced that the drop between run-in and 20 mg/day shown in the dose response curve can unambiguously be attributed to the fampridine treatment.

In conclusion, the efficacy of the 10 mg bid dosage regime and thus the subject-matter of claims 1, 4 and 7 cannot be directly and unambiguously derived from the disclosure of C30.

8.7 Document C28 is the publication of European patent application No. 11 160 247.0, a divisional of application No. 05 732 613.4 from which the patent in suit originated.

8.7.1 In its statement setting out the grounds of appeal (IV.6), appellant-opponent 1 contended that the patent in suit was not entitled to the first priority date of 9 April 2004 and the divisional application C28, which was entitled to this priority date, constituted prior art pursuant to Article 54(3) EPC. Paragraphs [0074] and [0075] of C28 anticipated the subject-matter of the request held to be allowable by the opposition division. The appellant's objection was not reiterated with regard to auxiliary request 1.

8.7.2 Since the description of C28 including paragraphs [0074] and [0075] is identical to the description of application No. 05 732 613.4, there is in fact no reason why the priority should be valid in one case and not in the other, and the passage in C28 should be regarded as prior art. Also, the cited paragraphs refer to aminopyridine rather than 4-aminopyridine. Contrary to the appellant's view, there can be no "poisonous divisional" effect (see also the principles set out in the Enlarged Board's decision, G1/15, OJ EPO 2017, 82).

9. Inventive step - auxiliary request 1

Starting point in the prior art

9.1 Inventive step has been assessed starting from the disclosure of document C27 (see point 8.5 above).

9.2 C27 reports on the respondent's MS-F201 trial, which was designed as a preliminary study with 36 subjects to explore the safety and efficacy of escalating doses of sustained-release 4-aminopyridine from 10 mg bid to 40 mg bid. C27 (see the paragraph bridging pages 45 and 46 and page 46) reports that the 4-amino-pyridine-treated group as a whole showed improvement in walking speed, including statistically significant improvement in the lower dosage range from 10 mg bid

to 25 mg bid; however, no separate individual analysis is provided as to how each dose of drug affected walking speed from baseline compared with placebo.

C27 further mentions that, after extensive consultation with a panel of expert MS neurologists and with the FDA (the US regulatory agency for pharmaceutical drugs), a larger clinical trial (the MS-F202 trial) had been initiated which was designed to compare three doses of 10, 15 and 20 mg bid and to assess their relative safety and efficacy over a treatment period of 12 weeks, with regard to an improvement in average walking speed (see C27: page 45).

Technical problem to be solved and solution

9.3 Claims 1, 4 and 7 of auxiliary request 1 require therapeutic efficacy of the 10 mg bid dosage regime for increasing the walking speed of MS patients, whereas document C27 does not disclose whether this specific dosage regime has therapeutic efficacy.

9.4 On the basis of the data analysis of the MS-F202 study presented in Example 5 of the patent in suit, the board is satisfied that the technical effect of applying the 10 mg bid dosage regime is acceptable efficacy combined with a favourable safety profile.

9.5 The technical problem to be solved was thus the identification of an advantageous dosage regime for 4-aminopyridine for increasing the walking speed of a patient with multiple sclerosis.

9.6 The solution to this problem is defined in claims 1, 4 and 7 of auxiliary request 1.

Obviousness of the solution

9.7 The appellants contended that determining the appropriate dosage of a known drug, let alone merely confirming the efficacy of the 10 mg bid dosage regime, would not have required inventive skill for the following reasons (points 9.7.1 to 9.7.5).

9.7.1 The person skilled in the art would routinely have sought to identify the lowest effective dose, in order to minimise the risk of adverse effects.

Since document C27 mentioned that a dose-finding trial designed to compare the three doses of 10 mg bid, 15 mg bid and 20 mg bid was underway (see C27, page 45, discussing the MS-F202 study), the person skilled in the art would also have had a reasonable expectation of success with regard to the lowest dosage of 10 mg bid included in that trial.

9.7.2 Furthermore, C27 already expressed doubts that the MS-F202 trial would have sufficient power for discerning statistically significant differences, and provided a solution for this trial defect, namely that of increasing the group size (see C27, page 45, fourth paragraph), stating:

> *"It is also possible that the clinical trial may not provide statistical significance on the primary endpoint but give us a clear indication of dose and group size to inform the design of two subsequent Phase 3 clinical trials that should provide sufficient pivotal data...".*

It would have been routine work for the person skilled in the art to follow this teaching and set up a clinical trial powered to confirm the expectation that the 10 mg bid dosage regime would have the desired therapeutic efficacy.

9.7.3 The responder analysis developed by the respondent was not mandatory in order to prove therapeutic efficacy. The data from phase 3 trials shown in Figures 1 and 2 of C22-Annex G (the prescribing information for the respondent's sustained-release 4-aminopyridine (10 mg) tablets Ampyra™) confirmed that a significantly greater proportion of patients taking 10 mg bid of the drug had shown increases in walking speed of at least 10%, 20% and 30% from baseline compared with placebo.

9.7.4 It was not even necessary to conduct a large-scale trial, either. According to document C3, a statistically significant therapeutic benefit of sustained-release 4-aminopyridine (17.5 mg bid) with regard to walking speed had been demonstrated with a group size of only ten subjects.

9.7.5 Moreover, as the results of the failed MS-F202 trial had not been published as prior art, they could not have lowered the expectations of the skilled person on the relevant date.

9.8 The board does not come to the same conclusion, for the following reasons.

9.8.1 The board considers that, on the basis of the information presented in C27, it would have appeared realistic to the skilled person to investigate the dosages of 10, 15 and 20 mg bid, with the primary endpoint being an improvement in average walking speed, since this was known to have been recommended by a panel of expert MS neurologists and by a relevant regulatory authority (FDA) and these dosages had been found to be of interest in a preliminary study (the MS-F201 study).

9.8.2 However, presumably due to the high intra-patient and inter-patient variability of disease symptoms (here:

walking speed) in the case of MS and the relatively high proportion of non-responders to 4-aminopyridine, it actually turned out to be exceptionally difficult in this case to provide the required proof of efficacy - as shown in Example 5 of the patent which presents data obtained in the MS-F202 study and as discussed in the respondent's declaration C20 (on this subject, see also points 2.1 to 2.11 above). The MS-F202 study serves not as prior art but as experimental evidence of this difficulty.

(a) The MS-F202 trial was designed as a parallel-arm study to investigate three doses of sustained-release 4-aminopyridine which had been found to be below the threshold for increased adverse effects.

The primary efficacy variable in the MS-F202 study was percent change in average walking speed during stable-dose treatment relative to baseline (placebo run-in) using the Timed 25-Foot-Walk test.

(b) It was recognised in the art that, due to the variability in MS, only a change of at least 20% in walking time reliably indicated a change in true function. 206 patients were randomised to the MS-F202 study. As explained by the respondent (see C33: point 14), the MS-F202 study was adequately powered to determine the efficacy of each dosage since the sample size was designed to have >80% power to detect a 20% or greater improvement in mean walking speed with an active treatment arm compared with placebo, at the 5% significance level, at each of the three doses.

(c) Nevertheless, the pre-planned statistical analysis did not, after all, provide the desired evidence of statistically significant differences in the primary efficacy variable between the groups

receiving the drug and the placebo group. Nor did the "protocol-specified responder analysis", which still identified responders according to the magnitude of response (see point 2.8 above, Figures 3 and 4 of the patent in suit).

(d) According to the respondent (see C33: point 14), even if the results from each of the three treatment groups of the MS-F202 study were pooled (sample size = 152 subjects), the change in walking speed would still not be found to be significantly increased compared with placebo.

(e) These data support the respondent's argument that, even with data obtained in an adequately powered dose-finding study, it was not straightforward to demonstrate and compare the efficacy of the three dosage regimes. Using conventional methods, the person skilled in the art would thus have failed to appreciate the benefit of the 10 mg bid dosage regime.

(f) In contrast, it is speculation to assume (as argued by the appellants) that the person skilled in the art carrying out a dose-finding study as suggested in C27 and relying on the magnitude of response for its analysis would not have encountered similar difficulties as the respondent.

9.8.3 Failure of a phase 2 trial such as MS-F202 would not have caused the person skilled in the art to simply set up, in spite of this result, a larger-scale trial with the same outcome variables, and nor is this suggested in C27. As pointed out by the respondent and the opposition division (see the decision under appeal, point 4.5.22 of the Reasons), such an approach would be contrary to both ethical and cost considerations.

9.8.4 Only by developing, post hoc, a new statistical technique (the "responder analysis") which focused on the consistency of response over several assessment visits rather than the intensity of response was the respondent able to prove that the 10 mg bid dosage regime is effective at increasing walking speed. The responder analysis is suitable for identifying response when a subsection of the treated group is not actually responding, and also eliminates background noise resulting from the fluctuating nature of MS symptoms. The analysis of the data with this tool also led to the conclusion that there are no notable differences in efficacy between 10 mg bid and the higher dosages. Also, the mean improvement in walking speed for the 4-aminopyridine responder group ranged from 24.6% to 29%, although responders were identified according to consistency of response and not magnitude of response (see paragraph [0107], table 12 and Figure 10 of the patent in suit). Given that 10 mg bid demonstrated the most favourable safety profile, it was identified as being superior to higher doses.

The appellants did not argue that the "responder analysis" methodology would have been obvious to the person skilled in the art and did not present prior art using this methodology.

9.8.5 The respondent also used the more reliable variable of consistency of response according to the new "responder analysis" as the primary outcome variable in the subsequent phase 3 trials MS-F203 (C21-Annex C) and MS-F204 (C21-Annex D), which confirmed its utility as well as the results on efficacy obtained in the MS-F202 trial.

9.8.6 Concerning the appellants' argument relating to small-scale studies and document C3 (see point 9.7.4 above),

it is evident that C3 reports on a small preliminary study that tested different outcome variables for their potential utility. One of the variables examined was the absolute difference in walking time (indicated in seconds) obtained in a crossover study with ten subjects in one single measurement after 1 week of treatment with 17.5 mg bid 4-aminopyridine (see C3: article abstract and Figure 1). The baseline appears to have varied, as the eight subjects who were able to walk eight metres at screening took 35.0 ± 25.3 seconds to do so on placebo. The improvement in walking speed observed in five of the patients was less than 5 seconds (including no improvement in one case). As the individual baseline values are not indicated, it cannot be verified what the results would be in percent change from baseline. In view of the small sample size, the variability of MS symptoms, the occurrence of non-responders and the evidence presented in Example 5 of the patent in suit the study described in C3 can only be considered insufficient.

9.8.7 Thus, the appellants' arguments failed to convince the board that the person skilled in the art would have been able to confirm the efficacy of the 10 mg bid dosage regime without difficulty and without resorting to the novel responder analysis based on consistency of response.

9.9 As a consequence, the subject-matter of independent claims 1, 4, 7 would not have been obvious starting from the disclosure of document C27.

Further possible starting points

9.10 Apart from document C27, the appellants also regarded documents C10 and C30 as suitable starting points for the assessment of inventive step.

9.10.1 As already mentioned (see point 8.2 above), C10, C27 and C30 all relate to the same study, namely the respondent's MS-F201 study. All these documents predate the completion of the MS-F202 study, which for the first time provided evidence of the efficacy of the 10 mg bid dosage.

9.10.2 The board considers that the disclosure of C10 is not more relevant than that of C27 and does not represent a more promising starting point for the assessment of inventive step (see also points 8.3 and 8.5 above for a detailed discussion of the content of both documents).

9.10.3 The same may be said of the disclosure of document C30 (see also point 8.6 above). As discussed above (see point 8.6.3), the additional figure presented in C30 (dose-response curve) is inconclusive regarding the efficacy of the 10 mg bid dosage regime, so C30 does not add any relevant information beyond the content of document C27.

9.10.4 In fact, C27 may even be regarded as more relevant than either C10 or C30, on account of its description of the general set-up and purpose of the MS-F202 trial, which confirms that the 10 mg bid dosage regime was about to be investigated for its therapeutic efficacy (see point 9.8.1 above).

9.10.5 Thus, the board's conclusion acknowledging an inventive step would not be any different if the assessment started from C10 or C30 instead of C27. As a consequence, a separate discussion of the approaches starting from C10 or C30, and a decision on the admission of the inventive-step approach starting from C30, are not required.

9.11 Document C3, which was favoured by the respondent as the starting point, relates to a small study with 10

patients receiving a higher dosage of 17.5 mg bid of sustained-release 4-aminopyridine. C3 does not disclose or suggest a dosage regime of 10 mg bid. It is thus less relevant than document C27 and would not have directed the person skilled in the art to the claimed subject-matter.

Conclusion on inventive step

9.12 For these reasons, the subject-matter of independent claims 1, 4, 7 and of the dependent claims of auxiliary request 1 involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:

   claims 1 to 7 of auxiliary request 1 filed with the reply to the statements setting out the grounds of appeal, dated 16 September 2014

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated